Atherosclerosis 240 (2015) 415–423

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

# Traditional Chinese lipid-lowering agent red yeast rice results in significant LDL reduction but safety is uncertain – A systematic review and meta-analysis

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ARTICLE INFO

*Article history:*
Received 22 January 2015
Received in revised form
2 April 2015
Accepted 2 April 2015
Available online 12 April 2015

*Keywords:*
Cholesterol
Cardiovascular risk reduction
Drug safety
Complementary and alternative medicine

ABSTRACT

*Objective:* To verify the safety and effectiveness of traditional Chinese red yeast rice-extract (RYR) for reduction of LDL cholesterol.
*Methods:* Systematic literature review and meta-analysis. Medline and EMBASE were searched until November 2014. We selected randomized studies in which RYR with a known content of the active substance monacolin K was tested against placebo or an active control group. Outcome measures were the effect of RYR on LDL cholesterol and incidence of adverse reactions with emphasis on liver and kidney injury and muscle symptoms.
*Results:* Twenty studies were analyzed. Quality of safety assessment was low in the majority of studies. RYR lowered LDL cholesterol with 1.02 mmol/L [−1.20; −0.83] compared to placebo. Effect of RYR on LDL was not different from statin therapy (0.03 mmol/L [−0.36; 0.41]). The incidence of liver and kidney injury was 0–5% and the risk was not different between treatment and control groups (risk difference −0.01 [−0.01; 0.0] and 0.0 [−0.01; 0.02]).
*Conclusions:* RYR exerts a clinically and statistically significant reduction of 1.02 mmol/L LDL cholesterol. Only when the mild profile of adverse reactions can be affirmed in studies with adequate methodology for safety assessment, RYR might be a safe and effective treatment option for dyslipidemia and cardiovascular risk reduction in statin intolerant patients.



## 1. Introduction

Statins are the most effective agents for improving lipid spectrum in order to reduce the risk of atherosclerotic disease [1,2]. While statins are generally well tolerated, a minority of patients suffers from side effects which diminishes therapy adherence and limits the full potential of risk reduction [3]. Several patients with a proven or perceived intolerance to statins and other established lipid lowering agents use alternative products to influence their lipid levels. Also other persons – even without dyslipidemia or increased cardiovascular risk – use alternative products to lower their cholesterol [4]. It is a common belief that these 'natural' agents do not have side effects. Of these agents, the traditional Chinese red yeast rice extract (RYR), has been studied in more detail. In this article we systematically review the evidence on the potential benefits and risks of RYR in order to determine its suitability in clinical practice.

Muscle symptoms are the major reason for statin intolerance. However, also non-specific symptoms such as fatigue, headache or gastrointestinal symptoms do contribute. The prevalence of statin intolerance may be up to 10% in clinical practice. Risk factors for statin intolerance include older age, female sex, renal disease, history of muscle symptoms and high statin dose [5]. As these risk factors tend to be exclusion criteria for clinical trials, prevalence of statin intolerance in trials is lower compared to clinical practice [6].

RYR is well-known in traditional Chinese medicine for its beneficial effects in cardiovascular disease [7]. RYR consists of powdered Monascus purpureus fermented rice. Its cholesterol

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http://dx.doi.org/10.1016/j.atherosclerosis.2015.04.004
0021-9150/

lowering effect is supported by empirical evidence and a plausible mechanism. Depending on the fermentation conditions of the rice and the Monascus strains used, HMG-CoA reductase inhibiting monacolins may be produced as metabolites. Several Monacolin subtypes were found in RYR products but the most profound subtype is monacolin K (MonK) which is identical to lovastatin [8]. In clinical trials, RYR doses varying from 200 mg to 4800 mg daily have been studied but monacolin content is not always reported. Also, commercially available supplements often lack a declaration of monacolin content [9]. Another concern is the Monascus purpureus metabolite citritin (CTN), which is a mycotoxin that is known to cause nephrotoxicity [10].

Although RYR is claimed to be a safer alternative to regular statins, structural similarity with lovastatin implies that similar adverse reactions can be expected. Indeed anaphylaxis, toxic hepatitis and rhabdomyolysis have been associated with the use of RYR [11–13].

In our study we determined to what extend RYR is an effective and safe agent for improving lipid profile. We systematically reviewed and meta-analyzed improvement of lipid profile, as measured by reduction of low density lipoprotein (LDL)-cholesterol and safety by assessing the incidence of adverse reactions.

**Added value to previous meta-analysis on red yeast rice extract**

The efficacy of RYR to reduce LDL cholesterol in patients with hyperlipidemia has been subject to meta-analysis before [14,15]. Our study extends the knowledge by a systematic and extensive review of evidence on the safety of RYR.

## 2. Methods

We applied methods as recommended by the Cochrane collaboration and the report is written in accordance with PRISMA guidelines [16,17]. The protocol was published online (http://www.crd.york.ac.uk/prospero, CRD42012003397).

### 2.1. Search strategy and selection criteria

We conducted a systematic literature search for randomized studies in which RYR with a known content of MonK was tested against placebo or an active control group for at least 4 weeks (Fig. S8). We searched EMBASE and Medline until November 2014. We did not apply language restrictions.

### 2.2. Data extraction and assessment of risk of bias

We selected eligible studies subsequently by title, abstract and full text (MG, CK). Any disagreement was solved by discussion or if required by the third reviewer. The authors extracted data on study design, lipid values and adverse reactions by a standardized data extraction form (MG, RT and HY for Chinese papers, MG and CK for English papers). Risk of bias was evaluated for all outcome domains. If lipid values were reported at more than 1 time point during follow-up, we included the 1st time point from 4 weeks in our analysis. Adverse reactions of special interest were kidney disease, liver abnormalities and myopathies. Other adverse reactions were arranged by organ system. Muscle symptoms were classified by symptoms and creatine kinase (CK) level [6].

### 2.3. Statistical analysis

A meta-analysis was planned on the change in LDL cholesterol, and on the risk of adverse reactions. Authors were contacted to complete missing data. When data on lipid values persisted to be unavailable we used imputation [17]. Influence of imputations was assessed through sensitivity analyses. We separately analyzed cholesterol lowering efficacy for studies comparing RYR with placebo or active controls. Statistical heterogeneity was assessed with the $I^2$-statistic. In case of heterogeneity we investigated potential causes by performing sensitivity analyses. If heterogeneity could not be reduced, we applied a random effects model. Excel 2010 and Review Manager were used for analysis. Results are presented as mean difference [95% confidence interval] unless otherwise specified.

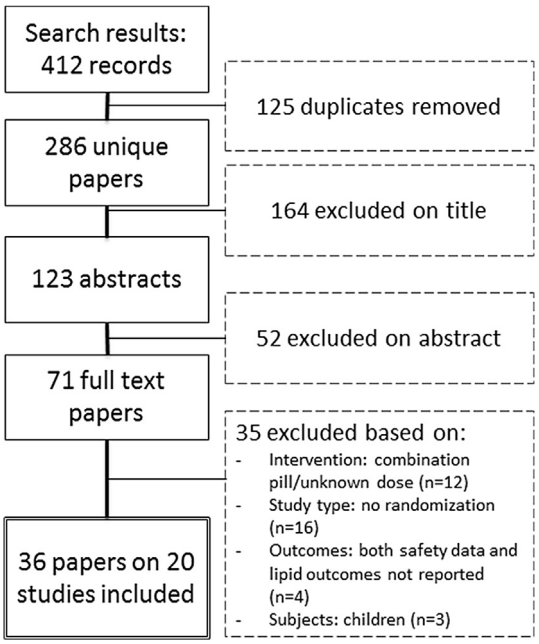


**Fig. 1.** Study selection. Flow chart of systematic literature search.

## 3. Results

Our search yielded 286 unique publications. After exclusion of studies not fulfilling selection criteria, we analyzed 36 publications on 20 studies (Fig. 1) [18–53]. Twenty-six papers were written in English and others were Chinese. The studies contained 6663 subjects in total, of which a large proportion was included in the Chinese Coronary Secondary Prevention Study (CCSPS) [21,22,33–37,40,41,48,53]. The CCSPS aimed to demonstrate a reduction in cardiovascular events and had a follow-up duration of 3.5 years. All other studies, which had surrogate parameters as primary outcome had a shorter follow-up (2–24 months). Five studies were conducted in Europe and North America and 14 studies were conducted in China. One study included patients in North America as well as China [42,43]. Three studies compared RYR to statin therapy, 13 studies compared RYR to inactive treatment and in 4 studies RYR was compared to a non-statin active control group (Table 1).

Dose of RYR varied from 1200 mg to 4800 mg per day, containing 4.8 mg–24 mg MonK. Four studies reported the constituents of RYR including different monacolin subtypes and possible toxins. In these studies, the MonK subtype was 57–75% of the total monacolin content. Six studies reported the MonK content without further specification and other studies referred to the RYR manufacturer. Citrinin concentration was determined in 3 studies and varied from <0.05 mg to <18 mg per daily dose.

**Table 1**
Characteristics of included studies.

| Study + Reference | Country | Participants | | | Interventions | Follow-up (weeks)[a] | Masking | Primary outcome | Funding |
|---|---|---|---|---|---|---|---|---|---|
| | | Main eligibility criteria | Age − mean (SD) | Sex − % male | | | | | |
| Becker 2009 [18,19] | US | DL, statin intolerance (n = 62) | 61 (8.5) | 36 | RYR 3600 mg (6.1 mg MonK) vs. placebo | 24 (12) | Double-blind | Lipid profile and RYR tolerability | Commonwealth of Pennsylvania (unrestricted) |
| Bogsrud 2010 [20] | Norway | DL, DM2 (n = 42) | − | − | 2400 mg RYR (4.8 mg MonK) vs. placebo | 16 (6) | Double-blind | Lipid profile | Pharmalogica AS (Scandinavian distributor of RYR) |
| CCSPS 2008 [21,22,33–37,40,41,48,53] | China | CHD (n = 4870) | 58.9 (10) | 82 | RYR 1200 mg (11.6 mg MonK) vs. placebo | 168 | Double-blind | Reduction of cardiovascular events | Chinese National Scientific and Technological Projects, WPU |
| Fan 2010 [23] | China | Non-alcoholic steatosis, DL (n = 84) | 54.5 (10) | 49 | RYR 1200 mg (10 mg MonK) vs. polyenylphosphatidylcholine 1.4 g | 24 (12) | No masking | Inflammatory factors (TNF-α, IL-6) | Unknown |
| Gong 2010 [24] | China | Hypertension, LVH (n = 60) | 57.7 (7.9) | 50 | RYR 1200 mg (10 mg MonK) + valsartan vs. valsartan only[b] | 104 | No masking | Left ventricular mass & heart rate turbulence | Unknown |
| Halbert 2010 [25] | US | DL, statin intolerance (n = 43) | 62.6 (8) | 26 | RYR 4800 mg (MonK 9.96 mg) vs. pravastatin 40 mg | 24 | Double-blind | Myalgia | Commonwealth of Pennsylvania (unrestricted), Center for CAM, National Institute on Aging |
| Heber 1999 [26] | US | DL (n = 88) | 61.5 (9) | 56 | 2400 mg RYR (4.8 mg MonK) vs. placebo | 12 (6) | Double-blind | Lipid profile | Pharmanex[c] (unrestricted). Heber is cochair of Pharmanex medical advisory board. |
| Hu 2006 [27] | China | CHD (n = 50) | 54.7 (4.25) | 62 | 1200 mg RYR (13.5 mg total monacolins) vs. placebo[b] | 6 | Double-blind | Lipid profile and CRP | Unknown |
| Huang 2006 [29] | China | CHD (n = 112) | 61.2 (16.7) | 52 | RYR 1200 mg (10 mg MonK) vs. probucol 1000 mg | 8 | No masking | Vascular endothelial function and redox state of vascular endothelium | Sichuan Science and Technology Department |
| Jian 1999 [30] | China | DL (n = 91) | 57.3 (10.8) | 63 | 1200 mg RYR (MonK 10 mg) vs. gemfibrozil 1200 mg | 8 | No masking | Lipid profile, thromboxane A-2 and prostacyclin | Unknown |
| Keithley 2002 [31] | US | HIV, DL (n = 14) | 42.5 (7.8) | 75 | RYR 2400 mg (MonK 4.8 mg) vs. placebo | 8 | Double-blind | Lipid profile, safety (plasma HIV RNA, CD4+ cells, liver function tests) | Pharmanex[c] provided study medication |
| Kou 1997 [32] | China | DL (n = 108) | 55.8 | 62 | RYR 1200 mg (10 mg MonK) vs. simvastatin 10 mg vs. placebo | 8 (4) | No masking | Change of lipid profile | Unknown |
| Lin 2005 [28,38] | Taiwan | DL (n = 79) | 46.4 (10) | 57 | RYR 1200 mg (MonK 11.4 mg) vs. placebo | 8 (4) | Double-blind | Lipid profile and safety | Y&B pharmaceuticals (unrestricted). |
| Liu 2011 [39] | China | DL, carotid atherosclerosis (n = 40) | 58.2 (5.7) | 60 | RYR 1200 mg (10 mg MonK) vs. lovastatin 20 mg[b] | 24 | No masking | Lipid profile and carotid intima-media thickness. | department of TCM Administration |
| Roth 2013 [42,43] | US & China | DL (n = 116) | 56.7 (10.8) | 26 | RYR 2400 mg (24 mg MonK) vs. RYR 1200 mg (12 mg MonK) vs. placebo | 12 | Double-blind | Lipid profile | WPU and Luye Pharma Group, China. 6/20 authors are employees of Luye Pharma group |
| Wang 1997 [44] | China | DL (n = 502) | 56.1 (0.6) | 59 | 1200 mg (2.4 mg MonK) vs. jiaogulan (TCM) | 8 (4) | Patients blinded | Lipid profile | 2/11 authors are employees of Pharmanex and 2/11 authors are employees of WPU. |
| Wang 2004 [45] | China | CHD (n = 105) | 59.9 (8.8) | 65 | RYR 1200 mg (10 mg MonK) vs. none[b] | 12 | No masking | | Unknown |

(*continued on next page*)

**Table 1** (*continued*)

| Study + Reference | Country | Participants | | | Interventions | Follow-up (weeks)[a] | Masking | Primary outcome | Funding |
|---|---|---|---|---|---|---|---|---|---|
| | | Main eligibility criteria | Age – mean (SD) | Sex – % male | | | | | |
| Wu 2006 [46] | China | Hypertension, DL (n = 100) | 56.7 (10.3) | 50 | RYR 1200 mg (MonK 10 mg) vs. placebo | 24 | Patients blinded | Endothelial function and inflammation (hs-CRP)<br>Lipid profile, myocardial fibrosis, left ventricular function, inflammation | Unknown |
| Yang 2009 [47] | Taiwan | DL (n = 47) | 53 (9.5) | 53 | RYR 1200 mg (16.4 mg MonK) + nattokinase 50 mg vs. nattokinase only[b] | 24 (4) | Double-blind | Lipid profile (change) | Industry-Academy Cooperation Project of the Ministry of Education, Taiwan |
| Zhao 2003 [51,52] | China | CHD (n = 50) | 58.3 (5.7) | 66 | 1200 mg RYR (MonK 10 mg) vs. placebo | 6 | Double-blind | Endothelial function and inflammation (hs-CRP) | WPU Biotech Co, Ltd, China. |

Abbreviations: DL = dyslipidemia. CHD = coronary heart disease. DM2 = type 2 diabetes. RYR = Red yeast rice extract. MonK = Monacolin K. TCM = traditional Chinese medicine.

[a] Number between brackets indicates the timepoint which was included in lipid analysis.

[b] 3rd intervention group in these studies was not included in this systematic review. WPU = WBL Peking University Biotech, Ltd, China.

[c] Pharmanex is a manufacturer of RYR. CAM = complementary and alternative medicine.

### 3.1. Quality of evidence

The majority of study reports did not contain sufficient information to judge all potential sources of bias. Risk of bias was evident in the assessment of adverse reactions which could have led to an underestimation of the incidence of adverse reactions in the RYR group (Fig. S1).

#### 3.1.1. Quality of safety assessment in included studies

Liver abnormalities and kidney injury were assessed in 14 and 8 studies respectively. Seven studies reported the incidence of intervention-associated increased liver transaminases whereas 5 studies reported average levels of transaminases. Three studies did not report numerical outcomes although liver transaminases were assessed. Three studies reported incident cases of kidney injury and 2 studies reported average creatinine before and after treatment. Four studies reported no numerical outcomes for kidney injury although it was assessed. All but 1 study did not report cut-off values for laboratory parameters of kidney or liver injury [38].

Muscle symptoms were assessed in 10 studies through CK and 2 studies also included anticipated symptom assessment through a validated questionnaire. Nine studies reported incident cases of muscle symptoms and 2 studies reported average CK before and after treatment.

Seventeen studies assessed other adverse reactions. Three studies roughly described the way symptoms were assessed and this was not described in all other studies. Four studies reported all adverse reactions and three studies only reported adverse reactions that led to discontinuation of study treatment. Two studies did not present numerical data and in 8 studies criteria for reporting events were not specified. An overview on the methodology and reporting of safety outcomes is given in Table 2.

### 3.2. Efficacy of RYR for improvement of lipid profile

The effect of RYR on lipid profile was moderate to considerable heterogeneous. We performed sensitivity analyses on studies with different doses of RYR and MonK, different durations of follow-up and different ethnic study populations. Heterogeneity remained and we performed all meta-analyses on lipid profile by random-effect analysis.

#### 3.2.1. RYR versus inactive control treatment

RYR was more effective for reduction of LDL cholesterol compared to placebo (Fig. 2). LDL decrease in the population treated with RYR varied from 0.5 to 1.59 mmol/L with a pooled estimate of −1.02 mmol/L [−1.20; −0.83] compared to placebo. Regarding changes in other lipid parameters, RYR resulted in a stronger reduction of total cholesterol compared with placebo (−1.0 mmol/L [−1.23; −0.77]). There was a small increase in high density lipoprotein (HDL) cholesterol of 0.07 mmol/L [0.03; 0.11] and a 0.26 mmol/L [−0.35; −0.17] decrease in triglycerides (Figs. S2–S4).

#### 3.2.2. RYR versus regular statin therapy

Three studies comparing RYR with MonK 10 mg daily to regular statin therapy (pravastatin 40 mg, simvastatin 10 mg, lovastatin 20 mg) did not show a significant difference between the interventions. The mean difference of change scores were 0.03 mmol/L [−0.36; 0.41] for LDL (Fig. 2) and −0.05 mmol/L [−0.28; 0.18] for total cholesterol (Fig. S2).

#### 3.2.3. RYR versus non-statin active control treatment

LDL reduction in RYR groups was 0.52 mmol/L [−0.9; −0.14] higher than the control group (Fig. 2). One study compared RYR to

**Table 2**
Method and reporting of safety assessment in included studies. Method of evaluation and way of reporting for the 3 safety outcomes of interest and other adverse reactions and patient reported symptoms. All evaluations were done at baseline and end of study unless reported otherwise.

| Study | | Kidney disease | Liver disease | Muscle symptoms | Patient reported symptoms |
|---|---|---|---|---|---|
| Becker | Method | Not reported/not assessed | AST and ALT | CK, muscle symptoms (Brief Pain Inventory, validated) and muscle weakness (dynamometry, validated). | Not reported |
| | Reporting | None | Means (BL, 12 wk, EOS). | Means (BL, 12 wk, EOS). Incident cases of intolerable persistent myalgia. | Incident cases |
| Bogsrud | Method | Creatinine and BUN (BL, 6 wk, EOS) | AST, ALT, GGT (BL, 6 wk, EOS) | CK (BL, 6 wk, EOS). No anticipated symptom assessment. | Not reported |
| | Reporting | No numerical data | No numerical data | No numerical data/1incident case | Incident cases, specified by group and type. |
| CCSPS | Method | BUN and Creatinine every 6 months | ALT and AST every 6 months | CK every 6 months. No anticipated symptom assessment. | Assessed, not specified. "Symptoms were registered." |
| | Reporting | Incident cases (subgroup, n = 2704 [37]) | See column 'kidney disease' | See column 'kidney disease' | See column 'kidney disease' |
| Fan | Method | Not reported/not assessed | AST, ALT, GGT, cholinesterase. | CK. No anticipated symptom assessment. | Assessed, not specified. |
| | Reporting | None | Means (BL, 12 wk, EOS). | Means in treatment group (BL, 12 wk, EOS). | 1 incident case (no other obvious AEs were found) |
| Gong | Method | Renal function every 3 months | Liver function every 3 months | Not reported/not assessed | Assessed every 6 months, not specified. |
| | Reporting | No numerical data | No numerical data | None | Incident cases (few) |
| Halbert | Method | Not reported/not assessed | Assessment of liver-associated enzymes | CK, muscle symptoms (Brief Pain Inventory, validated) and muscle weakness (dynamometry, validated). | Not reported |
| | Reporting | None | Outcome were assessed in t-test but numerical result is not reported | Incidence of different grades of myalgia. Means of muscle strength. | Incidence of adverse reactions categorized by type, per treatment group. |
| Heber | Method | BUN | ALT, AST, GGT, LDH | Not reported/not assessed | Not reported |
| | Reporting | Means and incident cases | Means and incident cases | None | Incident cases |
| Hu | Method | Not reported/not assessed | Not reported/not assessed | CK, no anticipated symptom assessment. | Not reported |
| | Reporting | None | None | Incident cases | None |
| Huang | Method | Not reported/not assessed | Not reported | Not reported/not assessed | Not reported |
| | Reporting | None | Incident cases | None | Incident cases |
| Jian | Method | Not reported/not assessed | Not reported/not assessed | Not reported/not assessed | Not reported/not assessed |
| | Reporting | None | None | None | None |
| Keithley | Method | Not reported/not assessed | Albumin, total and direct bilirubin, ALP, AST, ALT (BL, 2 wk, EOS). | Not reported/not assessed | Active questioning on any symptoms (2 wk, EOS). |
| | Reporting | None | Change in means from baseline to EOS. | None | No numerical data |
| Kou | Method | Creatinine and BUN (BL, 4 wk, EOS). | Liver palpation, ALT | CK (BL, 4 wk, EOS). No anticipated symptom assessment. | Not reported |
| | Reporting | Incident cases | Incident cases | Incident cases | Incident cases |
| Lin | Method | Not reported/not assessed | AST, ALT | CK (BL, 4 wk, EOS). No anticipated symptom assessment. | Assessment of severity and relation to study agent of any AE |
| | Reporting | None | Incident cases | Incident cases | Incident cases |
| Liu 2011 | Method | Creatinine and BUN | ALT | Not reported/not assessed | Not reported/not assessed |
| | Reporting | No numerical data | Incident case (1) | None | Incident cases |
| Roth | Method | Not reported/not assessed | ALT (BL, 4 and 8 wk, EOS) | CK (BL, 4 and 8 wk, EOS). No anticipated symptom assessment. | Open-ended questioning on any AE (4 and 8 wk, EOS). |
| | Reporting | None | Incident cases | Incident cases | Incident cases |
| Wang 1997 | Method | Creatinine and BUN | ALT | CK | Assessed (4 wk, EOS), not specified. |
| | Reporting | Not reported | Incident cases | Incident cases | Incident cases |
| Wang 2004 | Method | Not reported/not assessed | Not reported/not assessed | Not reported | Not reported/not assessed |
| | Reporting | None | None | Incident cases | Incident cases |
| Wu | Method | Not reported/not assessed | Not reported/not assessed | Not reported/not assessed | Not reported/not assessed |
| | Reporting | None | None | None | Incident cases |
| Yang | Method | Creatinine and BUN | AST, ALT | Not reported/not assessed | Assessed, not specified. |
| | Reporting | Means (BL, 4 and 12 wk, EOS). | Means (BL, 4 and 12 wk, EOS). | None | No numerical data |
| Zhao | Method | Not reported/not assessed | Not reported/not assessed | Not reported/not assessed | Not reported/not assessed |
| | Reporting | None | None | None | None |

Abbreviations: BL = baseline. wk = weeks. EOS = end of study. AE = adverse event. ALP = alkaline phosphatase. ALT = alanine transaminase. AST = aspartate transaminase. BUN = blood urea nitrogen. CK = creatine kinase. GGT = gamma glutamyl transpeptidase. LDH = lactate dehydrogenase.

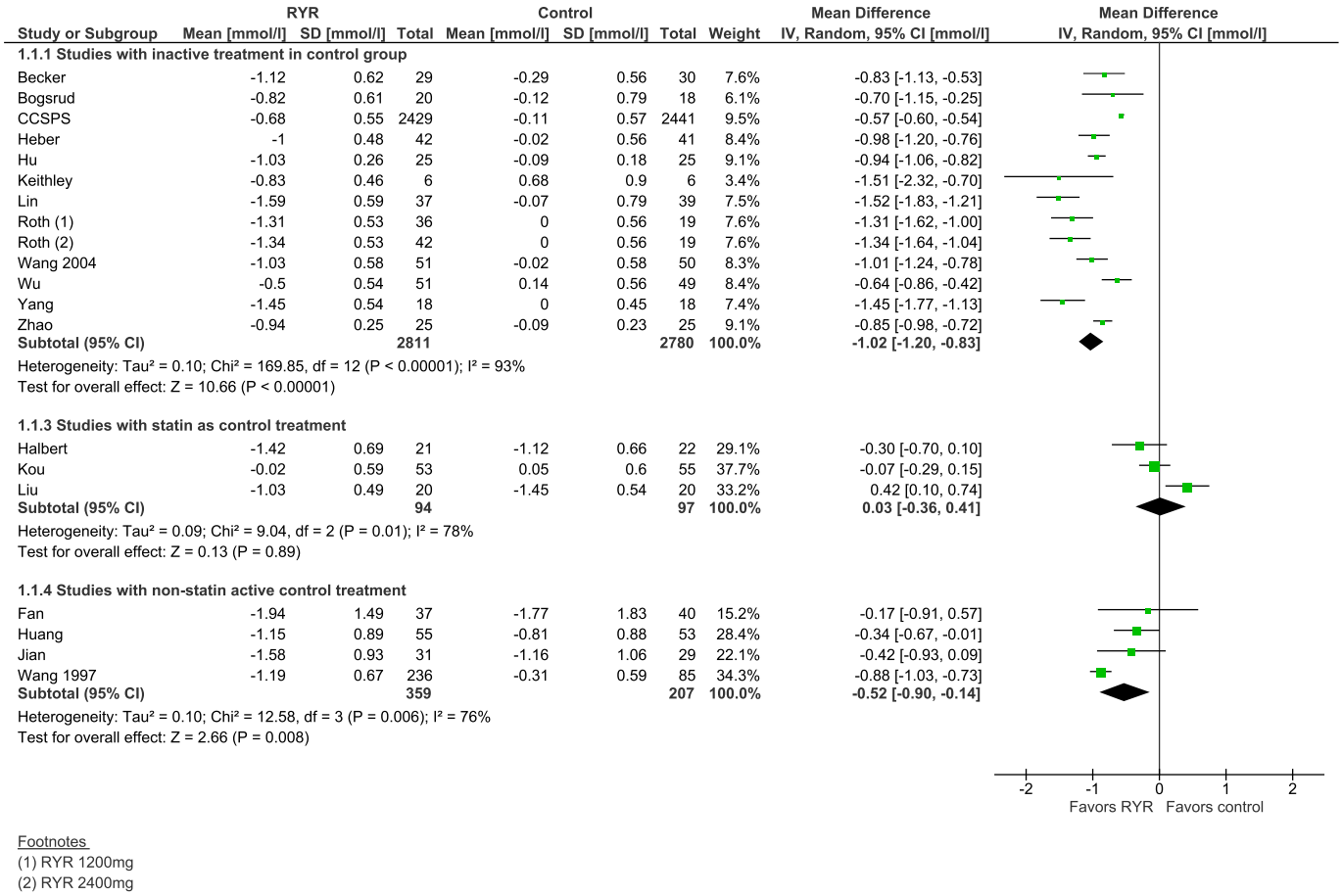


**Fig. 2.** Effect of red yeast rice (RYR) extract compared to inactive control treatment, statin therapy and non-statin active control treatment on change in LDL cholesterol from baseline.

gemfibrozil and 3 other studies treated the control group with herbal agents. In the study comparing treatment with RYR to gemfibrozil, the gemfibrozil group had a greater improvement of triglycerides and RYR was beneficial on all other lipid parameters (Fig. S4).

### 3.3. Safety of red yeast rice extract

#### 3.3.1. Kidney injury and elevation of liver transaminases

The incidence of cases of liver abnormalities and kidney injury was between 0 and 5% in both RYR and control groups. We did not observe a significant effect of RYR on the risk of liver abnormalities or kidney injury (Figs. S5–S6). Average level of liver transaminases in the RYR group decreased in all 5 studies in which it was reported.

#### 3.3.2. Muscle symptoms

The reported incidence of developing muscle symptoms was 0–23.8% for the population treated with RYR, versus 0–36% in the control groups. Rhabdomyolysis or myopathy with increased CK > 10 times upper limit of normal was not observed in any of the studies. The risk difference between RYR and control groups for myalgia was 0.00 [−0.01, 0.01] (Fig. S7).

One study compared myopathies between subjects treated with RYR versus pravastatin in a population selected for its increased risk on developing adverse reactions [25]. In this study the risk for developing muscle symptoms in the RYR group was 0.13 [−0.40; 0.15) lower compared to patients in the pravastatin group.

#### 3.3.3. Patient reported symptoms

Other adverse reactions and patient reported symptoms were classified by organ system (Table 3). The overview is limited by the fact that in most studies the methods for evaluating, defining and reporting adverse reactions were unclear and the risk of bias was often high. Four studies that reported all adverse reactions found an incidence of 30–76% of mild adverse reactions. In the other studies for which the criterion was unclear only 0–9% of subjects experienced an adverse reaction. Patients mainly complained of gastrointestinal and musculoskeletal symptoms. Besides, patients on RYR and controls reported nonspecific complaints (22/199 vs. 33/199).

## 4. Discussion

Our study shows that RYR reduces LDL cholesterol and suggests that the rate and type of adverse reactions are mild. Patients with an increased risk of adverse reactions on statins sometimes do tolerate RYR. However, the majority of studies did not contain enough data on safety.

The LDL lowering effect of 1.02 mmol/L compared to placebo is relevant since in a recent meta-analysis, a corresponding cardiovascular risk reduction of 15–20 % was described [54]. Especially for statin-intolerant patients, where alternatives for regular statin therapy to achieve LDL reduction are scarce, RYR can contribute to significant reduction in cardiovascular events.

In our analysis the average dose of MonK was 10.8 mg per day. Based on studies in which all monacolin subtypes were analyzed,

**Table 3**
Adverse reactions and patient reported symptoms. Absolute incidence of categorized adverse reactions in RYR/control group.*hypertensive subgroup (n = 2704, results were not reported on full population).

| | RYR/control → | **Sum** | Becker | Bogsrud | CCSPS* | Fan | Gong | Halbert | Heber | Huang | Kou | Lin | Liu | Roth | Wang 1997 | Wang 2004 | Wu |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Gastro-intestinal | Diarrhea | **7/1** | 1/0 | 2/0 | 0/0 | 1/0 | 0/0 | 2/0 | 0/0 | 0/0 | 0/0 | 0/1 | 0/0 | 0/0 | 0/0 | 1/0 | 0/0 |
| | GI discomfort | **42/19** | 0/0 | 1/1 | 10/3 | 0/0 | 3/1 | 3/0 | 0/0 | 0/2 | 2/1 | 0/1 | 1/0 | 15/10 | 5/0 | 2/0 | 0/0 |
| | Other GI | **2/0** | 0/0 | 1/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 1/0 |
| | **Subtotal** | **51/20** | 1/0 | 4/1 | 10/3 | 1/0 | 3/1 | 5/0 | 0/0 | 0/2 | 2/1 | 0/2 | 1/0 | 15/10 | 5/0 | 3/0 | 1/0 |
| Musculo-skeletal | Arthralgia | **14/7** | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 1/1 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 |
| | Weakness | **1/2** | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 1/2 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 |
| | **Subtotal** | **15/9** | 0/0 | 1/0 | 0/0 | 0/0 | 0/0 | 7/9 | 1/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 6/0 | 0/0 | 0/0 |
| Laboratory | LDH | **1/0** | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 1/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 |
| | Leukocytosis | **2/0** | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 2/0 | 0/0 | 0/0 | 0/0 |
| | Leukopenia | **0/1** | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/1 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 |
| | Hyperglycemia | **0/1** | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/1 |
| | **Subtotal** | **3/2** | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 1/1 | 0/0 | 2/0 | 0/0 | 0/0 | 0/1 |
| Infectious | Influenza | **1/0** | 0/0 | 1/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 |
| | Urinary tract | **9/4** | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 9/4 | 0/0 | 0/0 | 0/0 |
| | Pneumonia | **0/1** | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/1 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 |
| | **Subtotal** | **10/5** | 0/0 | 1/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/1 | 0/0 | 0/0 | 0/0 | 0/0 | 9/4 | 0/0 | 0/0 | 0/0 |
| Immunologic | Rash | **0/2** | 0/0 | 0/0 | 0/0 | 0/0 | 0/1 | 0/0 | 0/1 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 |
| | Alopecia | **2/0** | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 2/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 |
| | Allergic | **5/2** | 0/0 | 0/0 | 3/2 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 2/0 |
| | **Subtotal** | **7/4** | 0/0 | 0/0 | 3/2 | 0/0 | 0/1 | 2/0 | 0/1 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 2/0 |
| General | Dizziness | **2/2** | 1/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/2 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 1/0 | 0/0 | 0/0 |
| | Malaise | **1/0** | 0/0 | 1/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 |
| | Fatigue | **3/4** | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/3 | 0/0 | 0/0 | 3/1 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 |
| | **Subtotal** | **6/6** | 1/0 | 1/0 | 0/0 | 0/0 | 0/0 | 0/5 | 0/0 | 0/0 | 3/1 | 0/0 | 0/0 | 0/0 | 1/0 | 0/0 | 0/0 |
| CNS | Headache | **5/5** | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 2/2 | 0/1 | 0/0 | 0/0 | 0/0 | 0/0 | 3/2 | 0/0 | 0/0 | 0/0 |
| Cardiovascular | QT prolongation | **0/1** | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/1 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 |
| | Uncontrolled hypertension | **0/2** | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/2 |
| | Edema | **2/0** | 0/0 | 0/0 | 2/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 |
| | Erectile dysfunction | **0/3** | 0/0 | 0/0 | 0/3 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 |
| | **Subtotal** | **2/6** | 0/0 | 0/0 | 2/3 | 0/0 | 0/0 | 0/0 | 0/0 | 0/1 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/2 |
| Miscellaneous | Breast cancer | **1/0** | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 1/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 |
| | Unspecified | **22/29** | 0/0 | 0/0 | 3/3 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 17/25 | 0/0 | 2/1 | 0/0 | 0/0 | 0/0 |
| | **Subtotal** | **23/29** | 0/0 | 0/0 | 3/3 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 | 18/25 | 0/0 | 2/1 | 0/0 | 0/0 | 0/0 |

The values in bold denote the total amount of cases for each adverse event (as opposed to the results in the individual studies).

the total monacolin content is expected to be 6.1–8.1 mg higher. It is likely that some of these other monacolin subtypes contribute to HMG-CoA reductase inhibition and reduction of LDL cholesterol, although unknown to which extent. Other studies evaluating the efficacy of 10–20 mg of lovastatin resulted in an equivalent LDL reduction of 1.01–1.8 mmol/L [55].

Sometimes it is said that other non-statin components such as unsaturated fatty acids might explain the LDL lowering effect of RYR [56]. However, when taking into account the total monacolin content – which is probably underestimated when looking at MonK only – RYR produces the same magnitude of LDL reduction compared to regular statin therapy. RYR consists of carbohydrates (75%), monacolins (10–15%), fatty acids (1.5%), pigments (including citrinin) and trace elements [56]. In our conviction, it is unlikely that non-statin RYR components in the quantity present, exert a significant effect on LDL cholesterol or cardiovascular health via other pathways.

The low incidence of adverse reactions that we observed is probably an underestimation of the true incidence, due to a poor methodology of safety evaluation in the majority of studies. Furthermore, most studies were not endowed to make a judgment on the occurrence of adverse reactions in the general population: by excluding elderly people and various comorbidities, patients vulnerable for adverse reactions were systematically excluded. However, incidence of liver and kidney injury was assessed in 7 and 3 studies respectively and was similar to control groups. Two studies defined and assessed muscle symptoms clearly and found an acceptable rate of adverse reactions in statin intolerant patients [18,25]. Tolerance of RYR in these patients might be explained through a lower statin content of RYR. One study compared RYR containing 9.96 mg lovastatin to pravastatin 40 mg daily. While the correlation between statin dose and LDL reduction is generally low, adverse effects are more prevalent at higher statin doses [6].

Our results do not suggest that RYR results in different adverse reactions than the usual statin-associated adverse reactions. This conclusion is supported by case reports on RYR related adverse reactions, which describe mainly cases of usual statin-related adverse reactions. We investigated potential harm through the mycotoxin citrinin but we did not find an increased risk of kidney or liver injury. However, since RYR is sold as a dietary supplement, a registration study with thorough analysis of all possible adverse reactions has never been performed. For conventional statin therapy, incidence of muscle symptoms, liver and kidney damage has been analyzed over 45,000–290,000 person years [57–59].

Besides efficacy and safety, suitability of RYR in clinical practice is limited by financial and legal issues. RYR containing 10 mg MonK daily, is 3–12 times more expensive compared to regular brand HMG-CoA reductase inhibitors [60]. Since RYR is a food supplement, there are no uniform standards for its production and monacolin content. The US Food and Drug Administration prohibits RYR containing MonK but as RYR supplements are not registered this prohibition is not maintained adequately [61]. European regulation is limited to restrictions on health benefits that may be claimed through using food supplements. Within this framework, the European Food Safety Authority investigated and confirmed a beneficial effect of MonK on lipid spectrum [62]. However, since the monacolin concentration in over-the-counter available RYR is often uncertain, this claim may not be extrapolated to all RYR products.

A strength of our study is the detailed analysis of adverse reactions that could be attributed to RYR. RYR has been subject to meta-analysis before and these analyses resulted in comparable effects on lipid profile but none of the studies thoroughly assessed the safety of RYR [14,15]. A weakness of this meta-analysis were the differences in design and primary outcomes of the studies analyzed. The differences in the objectives of included studies led to differences in their designs, and probably resulted in the high level of heterogeneity for our primary outcome.

## 5. Conclusion

In conclusion, RYR exerts a 1.02 mmol/L reduction of low density lipoprotein cholesterol. The beneficial effect was achieved with 10.4 mg (±4.5) MonK daily. Although safety analysis of RYR was not a priority of the majority of studies analyzed, the incidence of kidney injury (evaluated in 2895 subjects), liver injury (evaluated in 2895 patients) and muscle symptoms (evaluated thoroughly in 105 patients) was found to be an acceptable rate.

To determine the suitability of RYR in clinical practice, monitoring of adverse reactions should become a priority of future trials which need to include patients at risk for statin intolerance. Only when the mild profile of adverse reactions can be affirmed, RYR might be a safe and effective treatment option for dyslipidemia and cardiovascular risk reduction.

## Contributors

- M.C. Gerards wrote the research protocol and was advised by V.E.A. Gerdes.
- M.C. Gerards and C.H.W. Koks selected and reviewed the studies in English.
- M.C. Gerards, Huixin Yu and Ruben Terlou reviewed the studies in Chinese.
- V.E.A. Gerdes was third reviewer in cases of disagreements.
- M.C. Gerards performed the analyses and wrote the manuscript, and was advised in this process by C.H.W. Koks and V.E.A. Gerdes.

## Competing interests

None.

## Funding

We did not request for, or receive funding for this research.

## Acknowledgments

We thank Dr. M.P. Bogsrud for his efforts to supply missing data. We thank the statistics helpdesk of the Amsterdam Medical Centre for their advice.

## Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.atherosclerosis.2015.04.004.

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